Migraine and Risk of Stroke in Young Women

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Citation:

Abstract
Purpose: To explore the relationship between migraine and incidence of stroke in young women by analyzing variables of oral contraceptive use, hypercoagulability, cardiac abnormalities, and silent brain infarcts. Method: Variables were reviewed through computerized databases and current literature examining evidence-based medicine studies specific to analyzing the incidence of strokes in women with migraines. Results: Six recent studies, four case control and two cohort studies, were identified. Research outcomes indicate that the risk of stroke is greater in women less than 35 years of age who had migraine with aura and who used oral contraceptives. Other pathophysiologic variables, which may link migraine to stroke, include hypercoagulability, cardiac abnormalities, and silent brain infarcts. Conclusion: Young women with migraine appear to be at higher risk of ischemic stroke than women without migraine. This risk is further increased by the co-existence of other established risks including hypertension, smoking, and oral contraceptives. Patent foramen ovale, silent brain infarcts, and hypercoagulability are underlying mechanisms that appear to link migraine to stroke. Clinical studies and research into the pathophysiology of migraine is essential to explain why migraine patients are at higher risk of ischemic stroke.

Background
Migraines are considered a benign disorder affecting 12% of the population with a three-to-one female prevalence. Stroke is an acute event occurring in two per 1000 people per year at a mean age of 70 and a two-to-one male prevalence. Surprisingly, patients under the age of 45 represent 5% to 13% of all patients with first onset stroke. Observational studies have shown an increased risk of stroke and a causal relationship between migraines and strokes in young women.

The purpose of this review of the literature is to achieve an understanding of the impact of migraines on the increased likelihood of stroke in young women. The significance of the relationship between migraine and stroke is critical to the treatment of migraine patients. Understanding the underlying mechanism of migraine is imperative and necessary to offer treatment plans that extend beyond current protocols. Similar to many chronic diseases, migraine headaches are disabling and often remove the individual from their ability to perform their activities of daily living. The relationship between migraine and stroke along with risk factors such as oral contraceptives, coagulation and platelet abnormalities, cardiac abnormalities, and silent brain infarcts will be reviewed.

Review of the Literature
The review of literature included results from six observational studies performed and a recent meta analysis of 14 studies specific to the relationship of migraine and stroke. The review also investigated pertinent causal factors such as oral contraceptives, hypercoagulability, cardiac abnormalities, and silent brain infarcts.

Several studies to date have assessed the risk of migraine for ischemic stroke. This review of literature was limited to those studies conducted within the last eleven years. The studies, chronologically detailed, evaluated the linkages between migraine and the occurrence of stroke in women ages 19-44. Careful clinical studies need to continue to determine the pathophysiology of migraine on a young woman’s predilection to stroke. Primary care providers need to be informed of the risks that increase stroke outcomes in young women with migraines.

Epidemiology
Migraines are predominantly a female condition with a
lifetime prevalence of 25% compared with 8% in men. The incidence of stroke is twice more common in men than women. The incidence of stroke in women, particularly those of childbearing years (ages 20 to 44) is therefore not only unexpected and unusual, but warrants further research to determine if a correlation exists between migraine and stroke outcome. Based on estimated values of strokes in women (5.5 per 100,000 woman years) and an adjusted odds ratio for ischemic stroke with migraine in the same population of 3.54 (95% CI, 1.30 - 9.61), a first stroke incidence in excess of 15 per 100,000 woman years is predicted among women with migraines. Women who experience migraines with an aura appear to be at a higher risk for stroke than those who experience migraines without aura. Other factors that have had multiplicative effects on odds ratios for an ischemic attack include use of oral contraceptives, high blood pressure, or smoking. Studies consider a migraine linked to a stroke if the patient has experienced a migraine within three days preceding the stroke. Studies have shown these women to be three times more likely to develop subsequent ischemic stroke.

Variables Consistent Across Literature
Variables consistent across studies of migraine and its influence on stroke included age, use of oral contraceptives, hypertension, smoking, and the diagnostic criteria for ischemic stroke. In all studies, stroke was confirmed by neuro imaging and is therefore considered objective data. Patients had both initial and follow up brain scans, either computed tomography (CT) or magnetic resonance imaging (MRI). Only patients with proven infarction on the follow up scan were considered as stroke patients.

Variables Inconsistent Across Literature
In contrast to diagnosis of strokes, criteria used for diagnosis of a migraine was more variable. While the classification of migraine was defined by the International Headache Society (IHS) criteria, the diagnosis was either clinical or patient reported. Additionally, studies did not consistently differentiate migraines with aura from migraines without aura. Several studies relied only on patient history or questionnaires. This subjective diagnosis will ultimately affect the correlation between specific migraine type and stroke risk. Other confounding variables not necessarily accounted for in all studies are obesity, alcohol, heart condition, education level, physician, and social class.

Relationship Between Migraine and Stroke
At least four direct correlations between migraine and stroke have been described. These relationships were not particular to a specific population but try to explain current theories of migraine and stroke. First, migraine attacks with aura led directly to ischemic stroke and were called migrainous infarcts. Second, the symptomatic migraine and stroke shared a common etiology. Third, the migraine attacks were caused by cerebral ischemia. This ischemia may or may not have been the direct cause of the stroke but rather a symptom of the stroke. The fourth relationship considers the migraine as the risk factor of the stroke itself.

The migrainous infarct is believed to be caused by severe hypo perfusion. When a migrainous infarct occurs, it has been observed during the aura stage of the migraine and a documented infarct in the relevant area was seen on neuro imaging. In these cases, no other cause for the infarct was apparent. Migrainous infarcts typically occurred in the posterior cerebral artery territory. The migraine-induced stroke has become a rare diagnosis after the International Headache Society (IHS) introduced strict definitions and diagnostic criteria.

The symptomatic migraine was by definition when the migraine was a cofactor in occurrence of a stroke. The cause of these migraines was considered to originate from an underlying vascular disease including a blood disorder, vessel wall abnormality, mitochondrial disorder, or a cardiac disorder. The conditions of cardiac disorders and blood disorders and their effect on migraine and stroke are detailed later in this review.

The third relationship between migraines and strokes concluded that migraines were caused by cerebral ischemia. A stroke event that presented with clinical features of a migraine attack with an aura was commonly reported as a severe headache. Continued research ensues to discover whether the migraine or the stroke occurred first.

The fourth relationship, migraine as an independent risk factor of stroke, has been currently debated in several studies and formed the basis for this review. Continued research will more effectively analyze the direct effect of migraines on stroke outcome.

Oral Contraceptives and Their Effects on Migraine
While the risks and benefits of estrogen have been well established, the effects of oral contraceptives on women were variable. Female hormones and the onset of puberty was the first indicator of increased prevalence of migraines in young females. Migraines also decreased in incidence during pregnancy, after age 40, and postmenopause. More prominent effects of estrogen have generally been linked to migraine with aura, suggesting that migraine with aura was a different condition than migraine without aura.

The effect of estrogens supports a connection between oral contraceptives and migraine. Most oral contraceptives triple a woman’s risk of venous thromboembolism, while dosage levels higher than 50ug or migraine headaches are considered risk factors for ischemic stroke. The high dose oral contraceptives and second-generation progestin were associated with the risk of cerebral thromboembolic attacks. The risk increased 2.5 times with estrogen dose increasing from 20 to 50 ug. Women taking low-dose oral contraceptives
with second-generation progestin had a 61% higher risk-association of cerebral thromboembolic attack than those using oral contraceptives with third-generation progestin.9

The significance of oral contraceptive use in women with migraines can bring increased risk of stroke due to thrombolytic events. Future research needs to better define this increased risk. Currently, contraceptives are not contraindicated in women with migraines since there is no apparent direct causal effect, but rather an additive risk from the oral contraceptive. The observed interactive effect of migraine and use of oral contraceptives was significant in young women who had strokes. However, this increased risk may also be attributed to confounding risk factors such as smoking.4

The International Headache Society Task Force on Combined Oral Contraceptives and Hormone Replacement Therapy suggested that women with increased risk of ischemic stroke consider progestin only hormonal contraception. These recommendations were not a standard because the evidence was considered low grade and randomized controlled clinical trials were not done. Data suggested that migraine in general had an odds ratio of three and that migraine with aura carried an odds ratio of six. The absolute risk remained low with estimates of 17-19 per 100,000 woman-years. The outcome of this study suggested further evaluation and/or stopping of oral contraceptives in women who had onset of persistent headache, new onset of migraine aura, increased headache frequency or intensity, or development of unusual aura symptoms, particularly prolonged aura.10

Hypercoagulability and Stroke in Young People
The cause of stroke in young adults was much more diverse than among the elderly. The most frequent stroke in young adults was the embolic stroke.2 The next most frequent was the lacunar infarction, representing almost 20% of all ischemic strokes in adults ages 30 to 40.11 While most lacunar infarcts were primarily the result of long-term arterial hypertension, research supported that hyper-coagulability and migraine were significant risk factors. Review over a five year period of 192 pre-menopausal women who had suffered cerebral vascular insult (65% hemorrhagic, 30% ischemic, and 5% unclassified) showed that women with migraine were more prone to a hypercoagulable state.2 The result of this small study brought attention to the risk profile of lacunar infarct in young women.

Additionally, coagulation and platelet abnormalities may have been significant contributors to the migraine process and perhaps a causal link between stroke and migraine. Abnormalities of coagulation have led to increased thrombolytic risk and strokes.12 While evidence of hemostasis and migraine has not been conclusive, studies have documented an increase of platelet function at the end of a migraine attack.9

Cardiac Abnormalities Effect on Migraine
A relation between cardiac abnormalities and the incidence of migraine has been reported. Research estimated that 25% of the population has a patent foramen ovale and this cardiac lesion was the most common cause for right-to-left shunt.13 Most patent foramen ovale were small and asymptomatic; however, the larger openings were cause for strokes in young adults because of increased risk for thromboembolism.14

A right-to-left shunt, most often caused by a patent foramen ovale, was found in almost half of migraine with aura patients. The incidence of migraine in stroke patients with patent foramen ovale ranges between 27% and 52%.15 This suggested that patent foramen ovale might have been causally related to migraine. Closure of the patent foramen ovale improved migraine with aura in patients with cerebrovascular disorders in noncontrolled observational studies.14 The association between right-to-left shunt and migraine in normal people and in stroke patients, as well as the benefit shown by repair of the defect, has strongly suggested a pathophysiologic link between migraine and patent foramen ovale.

While conducting research in scuba divers with a history of decompression illness, researchers noticed that divers often had a history of migraine with aura, not only associated with diving, but in everyday life. From this discovery, the medical records of 200 individuals were reviewed to determine an association between right-to-left shunt and migraine with aura. The outcome of this review showed 120 (60%) had a right-to-left shunt. The size of the shunt was graded as small in 18 cases (9%), medium in six cases (3%) and large in 96 cases (48%).10 The existence of a right-to-left shunt allowed small gas bubbles, typically filtered in the lungs, to embolize into neurological tissues.14 Symptoms of a neurological decompression illness are similar to that of migraine with aura and include headache, confusion, visual disturbances, numbness and tingling, tinnitus, and others.17

The observed linkages did not explain all migraine with aura, but did support the need for further research. Migraine in patients with patent foramen ovale may be due to any of the following speculative reasons. First, “showers of micro emboli crossing a patent foramen ovale may cause cerebral vasospasm and migraine.”18 Another thought was that shunting of activated platelets, serotonin, or other chemicals may have contributed to the migraines.15 Wilmhurst et al., 2000, theorized that “the patent foramen ovale allows vasoactive agents in venous blood to bypass the pulmonary filter and reach the systemic circulation.”14 If further research supports the relationship between patent foramen oval and migraines, then closure of the patent foramen ovale may reduce frequency and intensity of migraine attacks and subsequent migraine attributable strokes.19
Migraine as a Risk Factor for Silent Brain Infarcts

Silent brain infarcts were seen in 8% of patients with migraine. In contrast, people without migraine had only a 1% incidence of silent brain infarcts. Silent brain infarcts and white matter lesions were associated with an increased risk of subsequent stroke. Infarcts were small areas of dead brain tissue. White matter lesions were considered scar tissue in between the fibers connecting white matter to the grey matter of the brain. These lesions were referred to as silent brain infarcts because most people never realized they had occurred. Most silent infarcts occur in the cerebellum.

Silent brain infarcts increased the risk of stroke by greater than three times compared with those without infarcts. The presence of more severe white matter lesions also increased stroke risk. Both silent brain infarcts and white matter lesions reflected small-vessel disease. The Rotterdam Scan Study (2003) determined that “silent brain infarcts and white matter lesions were not just intermediates in the relation of vascular risk factors and the risk of stroke, but that these lesions may have been markers for other, yet unknown, factors that lead to symptomatic stroke.”

In view of the high prevalence of migraine, it was important to establish whether migraine was an independent risk factor for silent infarcts and white matter lesions. Both types of brain lesions increased the risk of clinical stroke events. Women with migraine with and without aura were at increased risk of silent infarcts and this risk increased with increasing attack frequency. Patients with migraine with aura and a high attack frequency were at the greatest risk. Traditional cardiovascular risk factors known to be associated with ischemic stroke or white matter lesions did not modify these risk estimates.

The underlying mechanism of a migraine that contributed to silent brain infarcts and white matter lesions may have been due to repeated or prolonged reduced perfusion pressure and reduced blood flow in large and/or small arteries of the brain. The activation of the clotting system combined with vasoconstriction could have exacerbated arterial or venous micro-embolism, thrombosis, or ischemia. Dehydration may have further worsened and contributed to formation of local thromboses. “It is also possible that excessive neuronal activation and neurogenic inflammation during migraine attacks lead to tissue damage. Cardiac abnormalities, such as patent foramen ovale or mitral valve prolapse, might also increase the risk of ischemic brain changes in patients with migraine.”

Case Study Results in Chronological Order

The most recent cohort study, 2004, estimated the incidence of ischemic stroke in young women at 3.56 per 100,000 per year. Women between ages 15 to 49 with a first diagnosis and supporting evidence of stroke between 1992 and 1998 were identified from the UK General Practice Research Database. A nested case control study was conducted to identify factors associated with an increased risk. Factors found to influence stroke risk were heart disease, heavy alcohol consumption, hypertension, use of oral contraceptives, and migraine. Researchers concluded that migraine significantly increased risk of stroke with an odds ratio of 2.33 (95% CI, 1.04 - 5.21). The Nightingale study did not distinguish between migraine with aura and migraine without aura.

In 2003, a case control study looking for an association between juvenile stroke and migraine determined that women were at risk of juvenile stroke with an odds ratio of 2.68 (95% CI, 1.25 – 5.75). The study enrolled 160 patients under the age of 46 years with first-ever ischemic stroke or transient ischemic attack and 160 strictly sex and age-matched controls. Further analysis divided the sample by those younger than 35 years of age and assessed an odds ratio of 3.26 (CI, 1.33 – 7.98). Researchers confirmed the findings of previous studies showing migraine was not only significant but also an independent risk factor for juvenile stroke. The study was unable to compare migraine with aura against migraine without aura due to a small sample of cases with aura.

Additional analysis using data from the World Health Organization (WHO) Collaborative Study of Cardiovascular Disease (CVD) and Steroid Hormone Contraception (SHC) (2002) concluded that the duration, frequency, recency, and type of migraine could alter the odds ratio on ischemic stroke. The study found 86 cases of first time diagnosis of stroke among women aged 20 to 44 years between June 1990 and January 1993 and matched them with 214 controls. Researchers concluded there is a relation between ischemic stroke and migraine with aura. Results included an adjusted risk of ischemic stroke in women with history of migraine, greater than 12 years, had an odds ratio of 4.61 (95% CI, 1.27 – 16.8). Women with migraine with aura had an odds ratio of 8.37 (95% CI, 2.33 – 30.1) and when migraine attacks were more frequent than 12 times per year, had an odds ratio of 10.4 (95% CI, 2.18 – 49.4).

An earlier and similar case control study in 1999, using the World Health Organization Collaborative Study in Cardiovascular Disease and Steroid Hormone Contraception along with a questionnaire, concluded that women of childbearing age have significantly higher risk of ischemic stroke associated with migraine. Subjects included 291 women aged 20 to 44 years with ischemic, hemorrhagic, or unclassified arterial stroke compared with 736 matched controls. One quarter of women who had a stroke reported a personal history of migraine. This data led to an adjusted odds ratio of 3.54 (95% CI, 1.30 – 9.61) for stroke in women with migraine history and an additional increased chance of stroke with current use of oral contraceptives, smoking, or high blood pressure.
In 1997, an epidemiological study of the United States examined the association between stroke and migraine and found both migraine and severe nonspecific headache to be associated with a significant increased risk for stroke. Data from the National Health and Nutrition Examination Survey (NHANES) included 20,729 people ages 25 to 74 years from 1971 through 1974. This data led to a migraine risk ratio associated with stroke at age 40 of 2.8 as compared with a risk of 1.7 at age 60. Researchers concluded migraine was a more significant risk factor in stroke at a younger age.23

The 1996 case control study included 308 patients aged 15 to 44 with either transient ischemic attack (TIA) or stroke and matched them with 591 age and sex matched controls. The findings concluded that migraine and cerebral ischemia risk was limited to women under the age of 35. Using the history of migraine and odds ratios in the study, the attributable risk of cerebral ischemia was 6% in patients below 45 years old and 20% in women below age 35.24

Results
Migraine in women below the age of 35 correlated with significant increase in risk of stroke. Migraine with aura and stroke incidence warrants further research to better understand the underlying pathophysiology.23 Women who experience migraine with aura were at a higher risk for stroke than those who experienced migraines without aura.24 Other factors that have had multiplicative effects on odds ratios for an ischemic attack included use of oral contraceptives, high blood pressure, or smoking.25 A meta-analysis of 14 studies concluded that the pooled relative risk of ischemic stroke was increased in people with migraine with a relative risk of 2.16 (95% CI, 1.89 – 2.48). The risk was higher with migraine with aura at a relative risk of 2.27 (95% CI, 1.61 – 3.19). Migraine without aura had a relative risk of 1.83 (95% CI, 1.06 – 3.15).25 The consensus of these studies and others conducted prior to 1996 concluded that migraine was a risk factor in developing stroke. Specifically, the risks increased with younger age (under 35) and with migraine with aura.

In the cohort studies, the risk of ischemic stroke was slightly more than double in patients with migraine. While the case control studies found increased risk in young women, researchers also reported increased risk by smoking and oral contraceptives. "Despite several possible biases, such as selection, diagnosis, recall, or publication biases, this increased risk is probably real, particularly with regards to migraine with aura in young women."21

Coagulation and platelet abnormalities, likely contributors to the migraine process, are a probable link between stroke and migraine.12 Though evidence linking hemostasis and migraine has been inconsistent, studies suggested an increase of platelet function at the end of a migraine attack.9

Cardiac abnormalities, such as patent foramen ovale, were known risk factors of stroke due to blood stasis, which can occur with a right-to-left shunt. Closure of the defect appeared to remove the stroke risk and simultaneously remove migraine attacks. Wilmhurst, Pearson, and Nightingale (2005) hypothesized "that the lungs may have a role in filtering substances in the venous blood that trigger migraine with aura. The blood that passes through the right-to-left shunt may be the cause of migraine attacks by circumventing the lung filter."26

The silent brain infarct was comparable to transient ischemic attack on stroke risk, with an approximate 20% chance of developing a stroke within four years.20 Women with migraine with and without aura were at increased risk of silent brain infarcts and this risk increased with higher migraine attack frequency. Patients with migraine with aura and a high attack frequency are at greatest risk for developing silent infarcts.6

Discussion
The purpose of this review of literature was to achieve an understanding of the impact of migraine on the likelihood of stroke outcome in young women. The results of these studies suggested that migraine is a risk factor for stroke in young women ages 19 to 44. There is however, reason to weigh the evidence cautiously in treatment of migraine patients. The individual studies, while conclusive that migraine is a factor, varied in the method of assessing patients with migraine history. This may have caused error in reporting of migraine. Some studies separated migraine with aura and others did not. This information may skew outcomes since migraine with aura appeared to have a higher correlation to stroke risk.

The Donaghy report in 2002 used data collected originally for the World Health Organization (WHO) Collaborative Study of Cardiovascular Disease (CVD) and Steroid Hormone Contraception (SHC). While database studies are not subject to recall bias, since collected information is at the time of consultation, they are subjected to information bias. This may have led to a low prevalence of reported migraine as compared with prospective studies that actively seek women with migraines. On the other hand, the Chang et al. report in 1999, using the same data from World Health Organization (WHO) Collaborative Study of Cardiovascular Disease (CVD) and Steroid Hormone Contraception (SHC) used a questionnaire, which relied on patient reporting previous migraine history and therefore was subject to recall bias, which may have caused the odds ratio numbers to be overestimated.

The prevalence of a patent foramen ovale in migraine patients was a particularly interesting discovery. A patent foramen ovale had an increased risk of cerebral embolism and the realization that closure of a patent foramen ovale reduced the risk for stroke and
serendipitously relieved migraine with aura exposed a lack of understanding of the migraine phenomenon. Currently, migraine is thought to be a vascular brain disorder. The analogy of neurological decompression illness and migraine with aura symptoms, though not specific to young women, was helpful in considering an alternative mechanism as a source for migraine with aura. The possibility that migraine with aura may be triggered by passage of venous blood through a right-to-left shunt of a patent foramen ovale will require a careful interventional study to test this hypothesis.

Lifestyle choices and use of oral contraceptives in women with migraine with aura needs careful attention. The patient examination should include assessment of migraine type, frequency, and other risk factors such as smoking, alcohol, and hypertension. Ideally, patients will document their migraines and be educated on the risk factors associated with migraine. The risk of oral contraceptives was consistent across all studies with an increased risk of approximately eightfold. Possible mechanisms for this association included hypercoagulability and cardiac abnormalities. Studies showed oral contraceptives to increase platelet formation and increase risk of stroke and migraine. Encouraging patients to stop smoking and increase exercise are still among the best advice for preventative treatment of stroke and may help relieve the symptoms of migraine as well.

Given the overlap of clinical symptoms in stroke and migraine, each condition may also mimic the other. Numerous studies, however, showed that migraine was an independent risk factor for stroke both during and separate from the migraine attack. Women of childbearing age and those with aura were at greatest risk of migraine-related stroke. Additional risk of stroke in migraineurs occurred in those using oral contraceptive pills and those who smoked cigarettes. Further research on the connection between migraine and stroke is essential. Many practitioners continue to treat migraine as a benign condition, considering it primarily an inconvenience with limited treatment.

The research into silent brain infarcts revealed possible etiologic mechanisms of migraine as cause of brain lesions. Further research with migraine patients and neuro imaging studies will not only provide important clues about the pathophysiology of migraine but also contribute to management guidelines for migraine. Based on the finding of higher risks in those with higher migraine attack frequency, it will be necessary to assess whether prevention of migraine attacks will also decrease the risk for brain lesions and stroke.

Many factors obscured the understanding of migraine and risk of ischemic stroke in young women. The concurrent use of oral contraceptives was the most evident at this time; however, the physical findings of vascular disorder and cardiac abnormalities need to be considered since migraine has been clinically tied to these conditions as well. Life style changes, such as exercise and smoking cessation, should be encouraged in migraine with aura patients since these have multiplicative effects on stroke risk. The vascular abnormalities brought on by medication commonly used, oral contraceptives, non-steroidal inflammatory drugs, herbs and vitamins can influence blood-clotting properties and further increase chances of stroke.

Conclusion
This review of the literature supported that migraine was an independent risk factor for stroke in young women. Women of childbearing age and those with aura were at greatest risk of a migraine-related stroke. The significance of these risks was consistent across all studies with an increased risk of approximately eightfold seen with oral contraceptive users. The absence of classic cardiovascular risk factors combined with evidence that migraine might be related to structural brain damage supported the possibility that migraine was more than a headache, but a chronic, progressive disorder.

Patent foramen ovale, silent brain infarcts, and hypercoagulability were underlying mechanisms that appeared to link migraine to stroke and will require careful controlled clinical studies to establish a more thorough understanding. Whether migraine was the result of underlying pathology, or simply a benign, inconvenient headache is essential information in providing a link between stroke and migraine. The relationship between patent foramen ovale and migraine will only be confirmed when randomized controlled trials demonstrate that closure of the septal defect reduces the risk of future migraine attacks or stroke.

Currently, there is no curative treatment for migraine and the pathophysiology is poorly understood. Specific research to include migraine studies will help provide better understanding of disease mechanisms and possibly discover curative solutions for migraine sufferers who may be at risk for ischemic stroke. Future study populations should include increased focus on women of childbearing age and those on oral contraceptives. Primary care providers need to be aware of the relationship and risks of stroke in young women with migraine.

References